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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,121	10/23/2000	Debra G. Gilbertson	00-53	2404

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,121	GILBERTSON, DEBRA G.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6, 9, 11-13, 15 and 17-25 are pending in the application.

Drawings

The drawings are acceptable for examination purposes.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-6, 9, 11-13, 15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of reducing cell proliferation or extracellular matrix production, treating fibrosis and reducing stellate cell activation in a mammal by administering a zvegf3 specific antibody. The specification discloses that cell proliferation, extracellular matrix production, and stellate cell activation are components of fibrosis (see p. 10, second paragraph of the specification). Therefore, the claims encompass, in general, antibody therapy. Specifically, the claims encompass antibody therapy for treatment of fibrosis.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass reducing proliferation and extracellular matrix production of any type of cell and treating any type of fibrosis (i.e. liver fibrosis, kidney fibrosis). The claims also encompass the administration of polyclonal Antibodies (Abs) or monoclonal Abs. The Abs can be humanized or non-humanized Abs, monoclonal or polyclonal. Furthermore, the claims encompass treating any fibrosis in any species of mammal, including humans.

The unpredictability of the art and the state of the prior art

There are two issues regarding the unpredictability of claimed treatment. 1) Is the treatment an effective treatment? 2) Can the treatment be successfully applied to any mammalian subject?

At the time of filing, the relevant art considered antibody therapy to be unpredictable. For instance, Clark ("Antibody humanization: a case of the 'Emperor's new clothes", Immunology Today, Vol. 21, No. 8:397-402; August 2000) teaches, "The antiglobulin response is perceived as a major problem in the clinical development of therapeutic antibodies.

Successive technical developments such as chimeric, humanized, and now fully human antibodies claim to offer improved solutions to this problem. Although there is clear evidence that chimeric antibodies are less immunogenic than murine monoclonal antibodies, little evidence exists to support claims for further improvements as a result of more elaborate humanization protocols." (See p. 397, abstract). Clark also teaches, "Immunogenicity of therapeutic antibodies is a significant problem and severely limits their widespread and repeated application to treat many diseases" and indicates several factors that are likely to influence immunogenicity of therapeutic antibodies (See p. 399: second paragraph, and Box I). Although humanization of antibodies attempts to reduce the immunogenicity of the antibodies, Clark points out that it might prove very difficult to generate tolerance to humanized or fully human antibodies (see p. 400, first paragraph), and, "For some therapeutic antibodies it seems likely that the problems of immunogenicity are likely to remain whatever the strategies chosen for their production" (See p. 401, under "Concluding remarks"). Therefore, the antibody therapy is an unpredictable art.

Li et al. ("Liver fibrogenesis and the role of hepatic stellate cells: New insights and prospects for therapy", Journ. Gastroent. Hepat. Vol. 14:618-633; 1999) indicates some of the possible future antifibrotic therapies, including down regulating stellate cell activation and promoting matrix degradation (see p. 618, abstract). Li points out, "The ideal drug would be one which is easily delivered and well tolerated, with high liver specificity and few adverse effects. This therapy should promote the resorption of excess interstitial matrix without abolishing the salutary effects of the normal hepatic ECM. The hope is not necessarily to abrogate fibrosis entirely, but rather to attenuate its development so that patients with chronic liver disease do not

succumb to the end the failure it creates (e.g. portal hypertension, ascites, liver failure). While no therapy yet meets these goals, the framework for developing such treatments is in place." (Emphasis added; see p. 623, fourth paragraph). It is noted that although a framework for developing antifibrotic therapy may have been in place, there was no guarantee that the untested therapies that were proposed would actually develop into a reliable therapy. For instance, the framework for cancer therapy has been in place for many years, yet there is still no highly predictable and reliable cancer therapy. Finally, Li indicates that several key questions need to be answered including "(i) what are the key genes initiating early stellate cell activation? (ii) What is the outcome of stellate cells during resolution of liver injury? Can they revert to the quiescent state? (iii) Are there any stellate-cell specific genes that can be used as genetic targets? (iv) What is the relationship, if any, between the loss of vitamin A and stellate cell activation and how can this be exploited therapeutically?" (See p. 326, under "Future Prospects"). Although applicants may have identified a possible target for fibrosis therapy (zvegf3), it is unlikely that all of the key genes involved in stellate cell activation have been identified. Furthermore, it also has not been determined if the activated stellate cells can be reverted to a quiescent state.

In summary, the art teaches that antibody antifibrotic therapy is unpredictable because there are several unresolved issues including 1) the host's tolerance for the therapeutic antibodies (regardless if the antibody is a polyclonal, monoclonal, chimeric, humanized, or fully human antibody); 2) the unknown negative effects of the treatment, such as complete abrogation of fibrosis; 3) the effect of the treatment on stellate cell fate; 4) the effect that other factors (i.e. other than zvegf3) may have on cell activation and ECM production (i.e. although the Ab may block one factor, there may be other unknown factors that must also be blocked). Therefore it is

unpredictable if the antibody treatment would be an effective treatment for any kind of fibrosis in any mammal.

Working Examples and Guidance in the Specification

The specification has no working examples, whatsoever, demonstrating administration of the zvegf3 antibodies to a mammal. There is no demonstration that treatment with the antibodies effectively reduces cell proliferation or extracellular matrix production, effectively treats fibrosis or reduces stellate cell activation in any mammal. The specification does not provide evidence sufficient to overcome doubts raised in the art with regards to methods of antibody therapy for fibrosis. No specific teachings regarding the use of the antibodies with any success is presented. There is no evidence provided that the antibodies are not immunogenic, and do not activate the host cells immune response to the therapeutic agent. There is no indication of the dosage amount or frequency required for effective treatment, an important aspect considering the teaching of Li that complete abrogation of fibrosis should be avoided. Therefore, there is no indication that the claimed treatment method effectively achieves any therapeutic benefit.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of the zvegf3 antibodies would require, initially, in vitro studies to demonstrate proof of principle. That is, prior to any therapeutic intervention, it would be necessary to create the claimed antibodies, show that the antibodies demonstrate the desired effects, and then show that the effects demonstrated in vitro could be replicated in animal models with some therapeutic effect, a series of showings not present in the specification. After successful experimentation in the animal models, the efficacy of the treatment would have to be tested in human subjects. This

would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. It would have to be demonstrated that the antibodies are tolerated by the patients, regardless if they are non-human, humanized, or fully human antibodies (as indicate by Clark).

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of antibody therapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
May 31, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER